Pergamon

Tetrahedron Letters 40 (1999) 6061–6064

TETRAHEDRON
LETTERS

$MgBr_2$-Directed *endo*-Selective Conjugate Addition of Organometallic Reagents to Enones Anchored on $Cr(CO)_3$

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Received 12 April 1999; accepted 29 June 1999

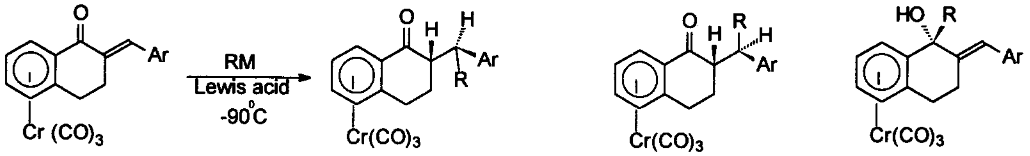
Abstract. Addition of RMgX or $RLi/MgBr_2$ to 2-arylidene-1-tetralone-$Cr(CO)_3$ complexes takes place in a conjugate manner with complete *endo* selectivity.

Nucleophilic addition at a benzylic or homobenzylic site of an arene tricarbonylchromium complex occurs commonly from the *exo* face (opposite to the metal carbonyl).[1] For stereochemically defined enone substrates, the presence of a Lewis acid in the medium can alter such steric preference.[2] For instance, conjugate addition of a strong nucleophile, such as organolithium reagent, to enones in the presence of $TiCl_4$ has been shown to occur from the *endo* face.[2b] In the absence of a Lewis acid, such reagents add exclusively in an *exo*-selective manner to the carbonyl functionality (1,2-attack) instead of the double bond (1,4-attack). In absence of additives, Grignard reagents were also expected to provide *exo*-selective 1,2-addition products from the same set of substrates. However, the results were dramatically different.

Contrary to expectation, a series of Grignard reagents added to the tricarbonyl-chromium anchored enones[2c] **1a-b** *in a conjugate manner* from the *endo*-face of the molecule exclusively (Scheme-1, Table-1, Entry 1-4).

PII: S0040-4039(99)01257-5

Scheme – 1



1a-b

1a: Ar = Ph
1b: Ar = $4\text{-Me-}C_6H_4$

2a-e

	Ar	R
2a	Ph	Me
2b	$4\text{-Me-}C_6H_4$	Me
2c	$4\text{-Me-}C_6H_4$	*n*-Bu
2d	Ph	$4\text{-Me-}C_6H_4$
2e	$4\text{-Me-}C_6H_4$	Ph

3a-b

	Ar	R
3a	$4\text{-Me-}C_6H_4$	*n*-Bu
3b	$4\text{-Me-}C_6H_4$	Ph

4a-b

	Ar	R
4a	$4\text{-Me-}C_6H_4$	Me
4b	$4\text{-Me-}C_6H_4$	*n*-Bu

Table – 1

Entry No.	Enone[a]	RM	Lewis Acid	Solvent[b]	Product[c]	Yield (%)[d]
1	**1a**	MeMgI in Et_2O	-	THF	**2a**	79
2	**1b**	MeMgI in Et_2O	-	THF	**2b**	82
3	**1b**	*n*-BuMgBr in Et_2O	-	THF	**2c**	80
4	**1b**	PhMgBr in Et_2O	-	THF	**2e**	89
5	**1b**	Me_2Mg in Et_2O	-	THF	**4a**	84
6	**1b**	Me_2Mg in Et_2O	$MgBr_2$	CH_2Cl_2	**2b**	80
7	**1b**	*n*-Bu_2Mg in Et_2O	-	THF	**3a**	84
8	**1b**	*n*-Bu_2Mg in Et_2O	$MgBr_2$	CH_2Cl_2	**2d**	86
9	**1b**	Ph_2Mg in Et_2O	-	THF	**3b**	77
10	**1b**	Ph_2Mg in Et_2O	$MgBr_2$	CH_2Cl_2	**2e**	87
11	**1a**	MeLi in Et_2O	$MgBr_2$	CH_2Cl_2	**2a**	78
12	**1b**	MeLi in Et_2O	$MgBr_2$	CH_2C12	**2b**	80
13	**1b**	MeLi in Et_2O	$MgBr_2$	THF	**4a**	82
14	**1b**	*n*-BuLi in hexane	$MgBr_2$	CH_2Cl_2	**2c**	89
15	**1b**	*n*-BuLi in hexane	$MgBr_2$	THF	**4b**	80
16	**1a**	$4\text{-Me-}C_6H_4Li$ in Et_2O	$MgBr_2$	CH_2Cl_2	**2d**	88
17	**1b**	PhLi in Et_2O	$MgBr_2$	CH_2Cl_2	**2e**	82

a: For characterization and stereochemistry of the enone double bond, see ref. 2a and 2c *b*: THF was used in most instances since the substrates are insoluble in diethyl ether or hexane. When reactions were carried out in the presence of $MgBr_2$, CH_2Cl_2 was used instead; in such cases, the ratio of ether and CH_2Cl_2 was maintained at 1:10 v/v; *c*: Characterization of all products have been reported in ref.2b *d*: isolated pure products.

This result was initially puzzling, for 1,4-addition on such a system was earlier[2] ascribed to an out-of-plane coordination mode of a Lewis acid to the ketone carbonyl group - such coordination obstructs approach of reagent to the ketone functionality from the *exo*-face. In the case of Grignard reaction, the only conceivable Lewis acid present in the medium could be $MgBr_2$ resulting from the Schlenk equilibrium.[3]

In order to ascertain the role of $MgBr_2$ in these reactions, salt-free dialkyl- and diphenylmagnesium were prepared[4] and treated with the substrates **1b**. Dibutylmagnesium added in a conjugate manner from the sterically unencumbered *exo* face in THF. When the substrate was pretreated with excess magnesium bromide, and THF was replaced by CH_2Cl_2 as a major component of the solvent, dibutylmagnesium yielded exclusively the *endo*-selective conjugate addition product (entry 7,8, Table-1). Similar behavior was observed for diphenylmagnesium (entry 9,10, Table-1). For dimethylmagnesium, the intrinsic preference for *exo*-selective 1,2-addition was modified into *endo*-selective 1,4-addition in presence of magnesium bromide (entry 5, 6, Table-1).

A non-coordinating solvent like dichloromethane is crucial for maximizing the effect of $MgBr_2$ – a donor solvent like THF, on the other hand, solvates this salt and nullifies its effect.

The role of $MgBr_2$ was further confirmed by carrying out a parallel set of additions using organolithium reagents added to the same substrates with and without $MgBr_2$ (entries 11-17, Table-1). For these reactions too, CH_2Cl_2 was used as solvent whenever $MgBr_2$ was present in the reaction medium – use of THF makes this additive ineffective (see: entries 12 *vs* 13, 14 *vs* 15, Table-1). When substrates were precomplexed with $MgBr_2$, addition of organolithium occurred in a conjugate manner with complete *endo* face selectivity.[7] In the absence of $MgBr_2$ the expected *exo*-selective 1,2-adducts were produced.

The similarity in product selectivity in the presence of titanium halides[2b] and magnesium bromide, strongly implies that Mg^{2+} can coordinate with the ketone carbonyl in an out-of-plane manner, and thereby direct the regio- and stereoselectivity of the reaction as does the Ti^{4+} ion. Out-of-plane coordination has been discussed[8] mainly for ions like Ti^{4+}, Sn^{4+} and Al^{3+}, where crystal structures have provided convincing evidence, or the steric outcome of reactions could be explained with the help of such a model. Magnesium is not usually associated with π-complexes. However, magnesium has vacant low lying *3d* orbitals, and they can participate in the formation of a π-bond.[9] To our knowledge, this is the first convincing example of out-of-plane bound magnesium ion to a carbonyl functionality, that completely reverses the steric course of nucleophilic addition as described above. In addition, these findings underscore the importance of the Schlenck equilibrium in Grignard reactions, which can either complicate the interpretation of results or provide a means to design stereodivergent routes for different stereoisomers from the same substrate, as in the present case.

Typical procedure for Grignard additions: To a suspension of the enone (1 mmol) in 7 ml THF at –90 °C, the Grignard reagent (1.2 mmol) in ether was added dropwise with stirring. After completion of the reaction (TLC, 15 min) reaction mixture was carefully quenched with degassed methanol (2 ml) at –90 °C. It was diluted with water and finally extracted with dichloromethane. The crude product obtained after removal of solvent was purified by flash column chromatography under nitrogen.

Typical procedure for $MgBr_2$ mediated additions: Dichloromethane (6 ml) was slowly introduced to a mixture of enone (1 mmol) and $MgBr_2$ (3 mmol) with stirring at -90 °C. Color of the solution became dark purple. It was stirred for 15 min. and then alkyllithium/ dialkylmagnesium in ether or hexane (1.2 mmol) was added. After completion of the reaction (TLC, 15 min.), the reaction mixture was quenched with degassed MeOH (2 ml), and allowed to reach room temperature. Usual work up followed by removal of the solvent afforded the crude product which was purified by flash column chromatography under nitrogen.

Acknowledgement : Two of us (V.M.S. and S.K.M.) thank the Council of Scientific and Industrial Research, New Delhi, for research fellowships.

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